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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,743	FISCHER ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,38,39 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34,38 and 39* is/are allowed.

6)☒ Claim(s) *47,51 and 52* is/are rejected.

7)☒ Claim(s) *48-50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The indicated allowability of claims 47 and 51-52 is withdrawn.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 47 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using an expression cassettes encoding SEQ ID NO:2 to produce late-flowering plants or expression cassettes comprising SEQ ID NO:1 or 5 to modulate development, does not reasonably provide enablement for methods of using a multitude of expression cassettes encoding DMT proteins with 80% identity to SEQ ID NO:2 or comprising 30 nucleotides of any nucleic acid encoding SEQ ID NO:2 to modify development in a plant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 20 April 2004 and 6 January 2005, as applied to claims 34-46. Applicant's arguments filed 29 October 2004 and 11 April 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to methods of delaying flowering by using a multitude of expression cassettes encoding DMT proteins with 80% identity to SEQ ID NO:2.

The instant specification, however, only provides guidance for characterization of *Arabidopsis dmt-1 and -2* mutants, which have fertilization-independent endosperm development,

created by T-DNA mutagenesis and use of the T-DNA to isolate the genomic clone, SEQ ID NO:1, which encodes SEQ ID NO:2 (example 1); isolation of *dmt-3*, made by another T-DNA insertion, and the conclusion that all mutant alleles are loss-of-function alleles (example 2); RNA analysis in *dmt/dmt* mutants to show that they have no *MEDEA* RNA expression (example 3), generation of transgenic plants in which DMT is overexpressed from the CaMV 35S promoter to create plants in which *MEDEA* RNA levels are increased (example 3); these plants are late-flowering (example 5); a BLAST search of SEQ ID NO:2 to show that DMT is a member of the HhH-GPD superfamily of DNA repair enzymes and has three domains that correspond to conserved regions of in other HhH-GPD family members (example 4); a BLAST search of databases to identify numerous related proteins and identification of consensus sequences for DMT, SEQ ID NOs:71-73 (example 4); speculation that DMT is a 5-methylcytosine glycosylase and that mutants have hypomethylation of the genome (example 5); and expression analysis of the DMT promoter, using a DMT promoter-GUS fusion gene (example 6).

The instant specification fails to provide guidance for nucleic acids encoding DMT proteins with 80% identity to SEQ ID NO:2 and methods of delaying flowering by using a multitude of expression cassettes encoding DMT proteins with 80% identity to SEQ ID NO:2.

The specification, on pg 18-19, suggests making conservative substitutions to produce variant proteins. However, making "conservative" substitutions does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577)

teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with 80% identity to SEQ ID NO:2. Making all possible single amino acid substitutions in an 1729 amino acid long protein like that encoded by SEQ ID NO:1 or 5 would require making and analyzing 19^{1729} nucleic acids; these proteins would have 99.9% identity to SEQ ID NO:2. Because nucleic acids encoding proteins with 80% identity to SEQ ID NO:2 would encode proteins with 345 amino acid substitutions, many more than 19^{1729} nucleic acids would need to be made and analyzed.

The specification states that SEQ ID NO:2 is related to endonuclease III, based on homology to a protein from *Deinococcus radiodurans* (pg 14, lines 18-20, and pg 40, lines 22-29, and pg 42, lines 4-24). However, this homology spans 191 of SEQ ID NO:2's 1729 amino acids and is only 31.4% similar. The *D. radiodurans* protein was identified in a genomic sequencing project as an endonuclease III by its having 53.3% identity to a protein from *Methanobacterium thermautotrophium* that was identified in a genomic sequencing project as an endonuclease III by its having 35% identity to a putative endonuclease III identified in a *Methanococcus jannaschii* genomic sequencing project (see GenBank Accession Nos. AE002073, AE000855 and Q58030). This was not followed back further, but the point is clear. Identification of the protein of SEQ ID NO:2 as an endonuclease III or a related protein solely by

homology to a series of putative endonuclease III proteins, and without other supporting data, like enzymatic activity studies, is speculative at best. Duggleby (1997, Gene 190:245-249) teach that "the function of any DNA sequence, whose identity is based solely on homology, can only be proven by experiments designed to evaluate that function" (pg 248, left column, paragraph 4). Additionally, an endonuclease III gene from *Arabidopsis* has been cloned (Roldán-Arjona et al, 2000, Plant Mol. Biol. 44:43-52). That protein has a very different sequence and is much shorter than the protein of SEQ ID NO:2.

The specification speculates, based on putative presence of a protein motif, that the protein encoded by the instant nucleic acid is an endonuclease III or a glycosylase (pg 42, lines 4-24), particularly a 5 -methylcytosine glycosylase (pg 44, lines 1-24). This conclusion is partly drawn because a mutation in an unrelated gene results in a reduction in genomic cytosine methylation and also results in phenotypic abnormalities in floral phenotype (pg 12-23). The specification also found weak homology between SEQ ID NO:2 and a series of protein fragments in the sequence databases and used those sequences to derive three consensus sequences, DMT Domains A, B and C (pg 42, line 24, to pg 43, line 28). However, the instant specification provides no evidence that SEQ ID NO:2 or any of these other proteins have the putative enzymatic function. Thus, it is not clear that DMT affects DNA methylation.

The specification teaches no assay to determine if any of the proteins encoded by nucleic acids encoding proteins with 80% identity to SEQ ID NO:2 have "DMT" activity.

No evidence is provided that any sequence not identical to SEQ ID NO:2 would modulate expression as claimed.

As the specification does not describe the transformation of any plant with any nucleic acid encoding a protein that has 80% identity to SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with a delaying in flowering time, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that with respect to the function of DMT, they submit Choi et al and Xiao et al, who show that the proposed glycosylase domain of DMT has a large number of conserved amino acids with known DNA glycosylases; one of skill in the art could use the sequence conservation with glycosylases to introduce changes into SEQ ID NO:2 (29 October 2004 response pg 9-10).

This is not found persuasive. Choi et al and Xiao et al both propose several possible functions of DMT (Choi et al, pg 8, right column, paragraph 4; Xiao et al, paragraph spanning pg 898-899), but do not know what that function actually is. Furthermore, Choi et al teaches that DMT has much dissimilarity with other Arabidopsis glycosylases (pg 8, right column, paragraph 3), suggesting that homology to glycosylases is not sufficient for making proteins with 80% identity to SEQ ID NO:2. Lastly both Choi et al and Xiao et al were published after the filing of the instant application and cannot be related upon for enablement.

The specification does not teach the function of DMT. The specification only states that SEQ ID NO:2 is related to endonuclease III, based on homology to a protein from *Deinococcus*

radiodurans (pg 14, lines 18-20, and pg 40, lines 22-29, and pg 42, lines 4-24) and speculates, based on putative presence of a protein motif, that the protein encoded by the instant nucleic acid is an endonuclease III or a glycosylase (pg 42, lines 4-24), particularly a 5-methylcytosine glycosylase (pg 44, lines 1-24). Choi et al teaches that DMT is not a 5-methylcytosine glycosylase (pg 8, right column, paragraph 4).

Applicant urges that the exact scope of sequence identity was already issued in the parent application, now US 6,476,296 (29 October 2004 response pg 10; 11 April 2005 response pg 6).

This is not found persuasive. Each case is examined independently.

4. Claims 47 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 20 April 2004 and 6 January 2005, as applied to claims 34-46. Applicant's arguments filed 29 October 2004 and 11 April 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to a method of using any of a multitude of DNA molecules that encode "DMT" proteins with 80% identity to SEQ ID NO:2. In contrast, the specification only describes a method of using a coding sequence from *Arabidopsis* that comprises SEQ ID NO:1. Applicant does not describe other nucleic acids encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Because the sequences are not described, the method of using the sequences to modulate development in a plant is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that the specification "teaches that DMT affects methylation whose structural basis is related to homology to an endonuclease [sic]" and the protein comprises a leucine zipper and nuclear localization signal sequence; thus sufficient structural function information is provided (29 October 2004 response pg 11).

This is not found persuasive. Words appear to be missing from applicant's argument. However, similarity to enodnucleases is not specific, given that there are a vast number of different kinds of endonucleases. Leucine zippers and nuclear localization signal sequences are common to a vast number of proteins of widely divergent functions, and are not sufficient to describe the claimed nucleic acids.

The written description guidelines (see example 14) teach 95% identity in which a single species identified is representative of the genus, the instant application does not provide this degree of specificity and thus does not provide an adequate written description of the claimed invention.

Applicant urges that the exact scope of sequence identity was already issued in the parent application, now US 6,476,296 (11 April 2005 response pg 6).

This is not found persuasive. Each case is examined independently.

5. Claims 48-50 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. Claims 34, 38 and 39 are allowed.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (571) 272-0745.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Anne R. Kubelik, Ph.D.
August 11, 2005